A randomised phase II study of Osimertinib and bevacizumab versus bevacizumab alone as second-line targeted treatment in advanced NSCLC with confirmed EGFR and acquired T790m mutations: the European Thoracic Oncology Platform (ETOP 10-16) Booster trial

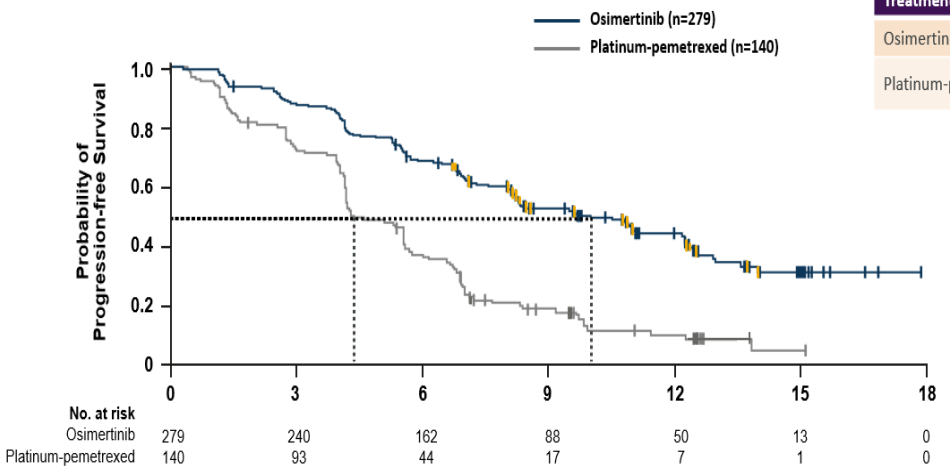
R. A. Soo et.al

Dr. Sunil Chopade

Consultant Medical Oncologist, Mumbai

Second line treatment of EGFRm T790m NSCLC

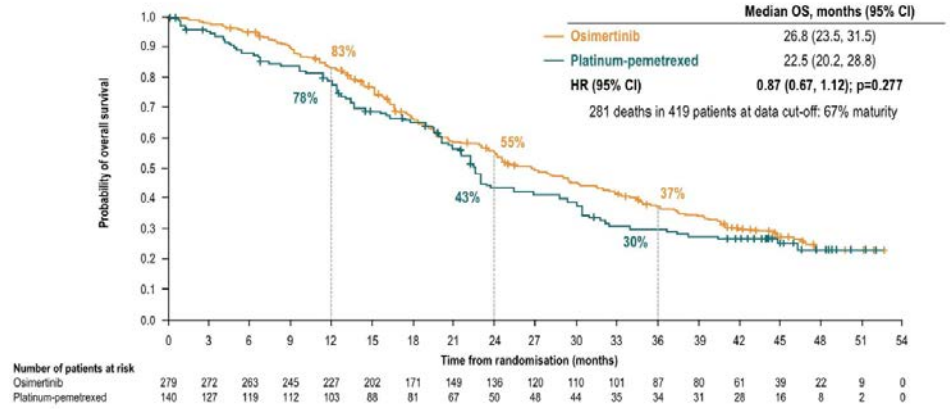
AURA3 PFS



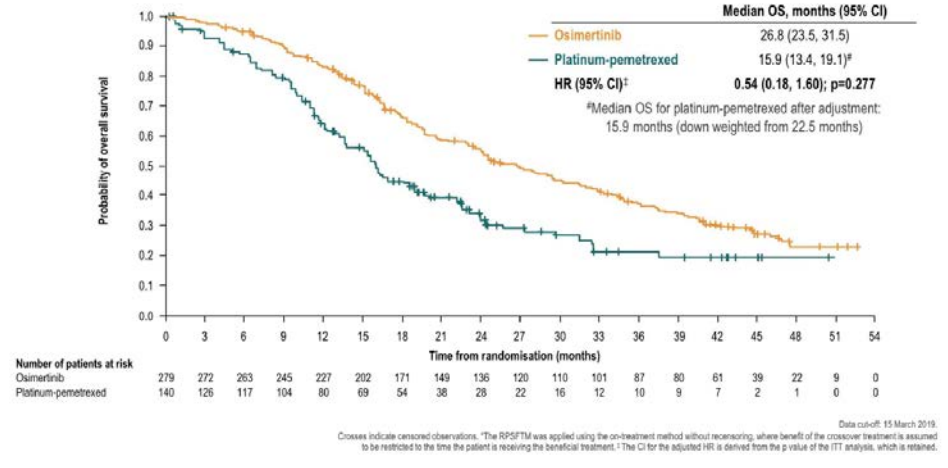
Treatment Group	Median PFS, months (95% CI)
Osimertinib	10.1 (8.3-12.3)
Platinum-pemetrexed	4.4 (4.2-5.6)

- Analysis of PFS by BICR was consistent with the investigator-based analysis
  - Median PFS: 11.0 vs 4.2 months
  - HR (95% CI): 0.28 (0.20-0.38), *P*<0.001

AURA3 overall survival



AURA3 overall survival with crossover adjustment*



How can we further improve survival in T790m?
Rationale for the Booster Trial

Vascular endothelial growth factor (VEGF) plays a critical role in tumour angiogenesis and has been shown to interact with EGFR-signalling pathways.

Increased VEGF levels in EGFR-mutant NSCLC were associated with resistance to EGFR inhibition.

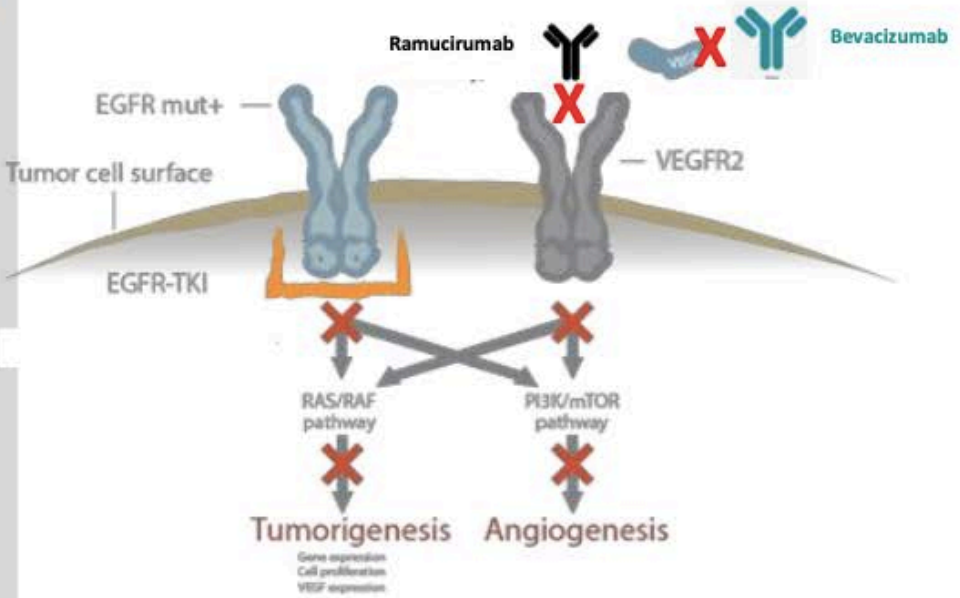
In preclinical studies, the combination of anti-VEGF therapy and EGFR TKIs has demonstrated synergistic anti-tumour activity, overcoming resistance to anti-EGFR therapy.

Several studies of anti-angiogenic agents in combination with erlotinib have shown to prolong PFS as compared to erlotinib monotherapy, in the first-line treatment of advanced EGFR-mutant NSCLC.

The objective of this randomised phase II study was to assess the efficacy of the combination of osimertinib and bevacizumab versus osimertinib in terms of PFS, in patients with advanced EGFR-mutant NSCLC with an acquired T790M mutation, after failure of previous EGFR TKI treatment.

How do the two agents actually work together to enhance PFS?

- Anti-angiogenic therapy can transiently normalize the tumor vessels network, improving drug delivery and efficacy.[1]
- Evidence of cross talk between EGFR and angiogenic pathway:
  - Epidermal growth factor receptor mutation enhances expression of vascular endothelial growth factor in lung cancer.[2]
  - Combined VEGFR and EGFR blockade overide primary or acquired resistance to EGFR TKIs.[3]



Ross Soo, MB, BS; PhD; FRACP

1. Jain Nature reviews. Neuroscience 2007; 2. Hung Oncol Lett 2016; 3. Naumov Clin Cancer Res 2009

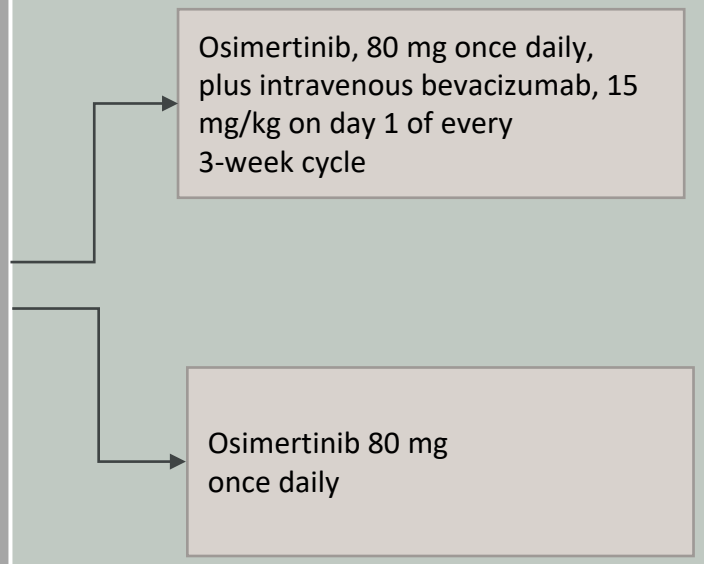
What are the results?

Study	ORR, %	DoR (m)	PFS (m)	PFS (HR)	OS (HR)	AE leading to discontinuation, %
FLAURA	80 v 76	17.2 v 8.5	18.9 v 10.2	**0.46 (0.37-0.57)**	**0.79 (0.64-0.99)**	13 v 18
JO25567	69 v 64	13.3 v 9.3	16.0 v 9.7	**0.54 (0.36-0.79)**	0.81 (0.53-1.23)	17 v 18
NEJ026	72 v 66	NR	16.9 v 13.3	**0.63 (0.43-0.91)**	1.00 (0.68-1.48)	19 v 15
CTONG1509	87 v 85	16.6 v 11.1	17.9 v 11.2	**0.55 (0.41-0.73)**	0.92 (0.69-1.23)	24 v 3
RELAY	76 v 75	18.0 v 11.1	19.4 v 12.4	**0.59 (0.46-0.76)**	0.83 (0.53-1.30	13 v 11
ALLIANCE	81 v 83	NR	17.9 v 13.5	0.81 (0.50-1.31)	1.41 (0.71-2.81)	26 v 0
BOOSTER	55 v 55	14.5 v 16.6	15.4 v 12.3	0.96 (0.68-1.37)	1.03 (0.67-1.56)	25 v 4
WJOG8715	72 v 55	NR	9.4 v 13.5	1.44 (1.00-2.08)	1.02 (0.43-2.44)	28 v 12

Ross Soo, MB, BS; PhD; FRACP

Methodology

- Pathologically confirmed non-squamous NSCLC harbouring a common sensitising EGFR mutation (exon 19 deletion or exon 21)
- Stage IIIb/IIIc) or IVa/IVb according to AJCC 8th edition, confirmed T790M mutation detected in tumour tissue or circulating tumour DNA (ctDNA) after disease progression upon EGFR TKI therapy.
- Previous exposure to a maximum of one line of platinum-based chemotherapy
- WHO status 0-2
- Presence of measurable or evaluable disease and adequate organ function.



Primary endpoint – PFS

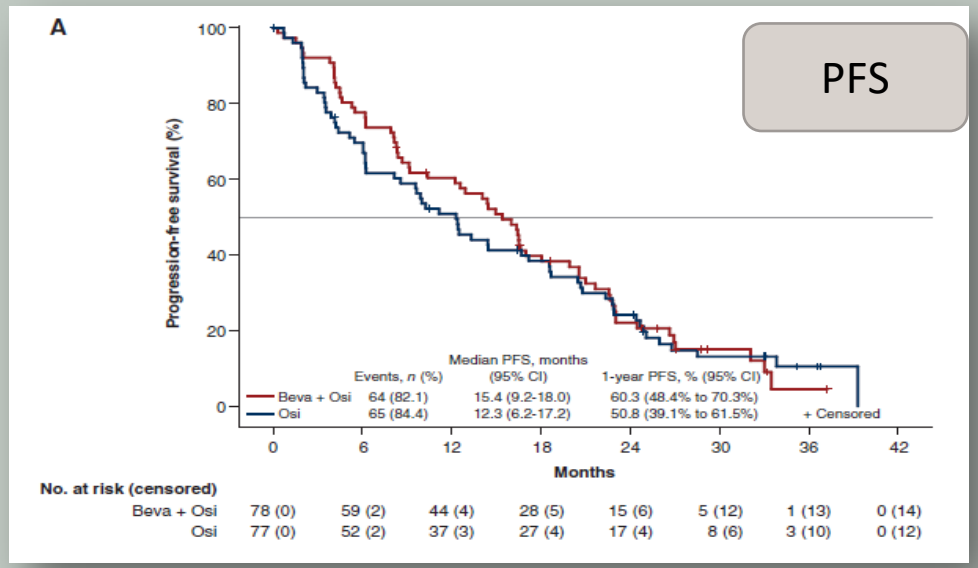
Secondary endpoints-
ORR
DCR
OS

Exploratory endpoints-
TTF
DOR
DOCB (duration of clinical benefit)

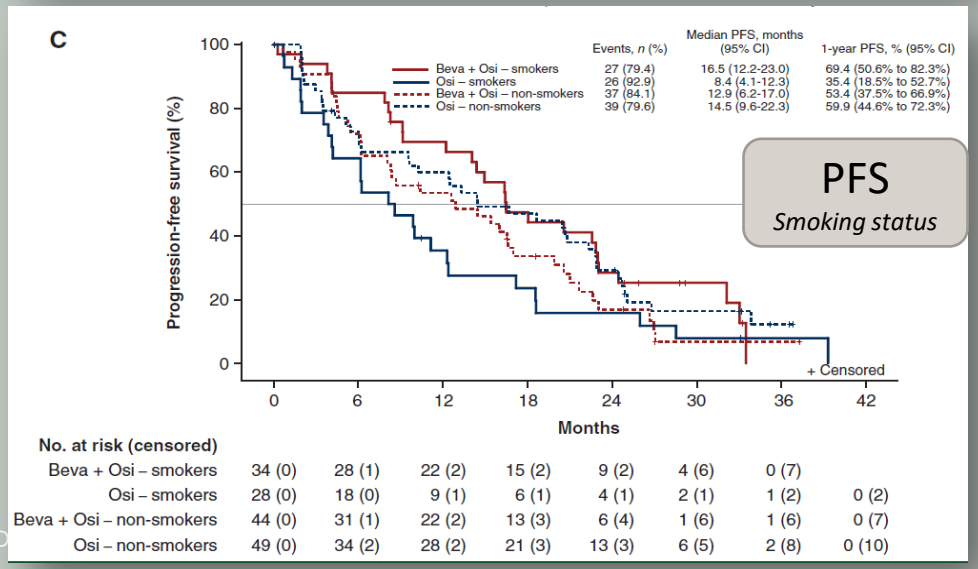
Baseline Characteristics

Characteristic	Osimertinib/bevacizumab (*n* = 78)	Osimertinib (*n* = 77)	All patients (*N* = 155)	*P* value
Age at randomisation, years				0.76[a]
Median (range)	68 (34-85)	66 (41-83)	67 (34-85)	
Sex, *n* (%)				0.74[b]
Male	31 (39.7)	28 (36.4)	59 (38.1)	
Female	47 (60.3)	49 (63.6)	96 (61.9)	
Ethnicity, *n* (%)				>0.99[b]
Asian	32 (41.0)	31 (40.3)	63 (40.6)	
Non-Asian	46 (59.0)	46 (59.7)	92 (59.4)	
ECOG performance status, *n* (%)				0.60[b,c]
0	22 (28.2)	25 (32.5)	47 (30.3)	
1	51 (65.4)	48 (62.3)	99 (63.9)	
2	5 (6.4)	4 (5.2)	9 (5.8)	
Smoking status, *n* (%)				0.41[b,d]
Current (still smokes cigarettes)	4 (5.1)	1 (1.3)	5 (3.2)	
Former (smoked ≥100 cigarettes in the past during the whole life)	30 (38.5)	27 (35.1)	57 (36.8)	
Never smoker (smoked 0-99 cigarettes during the whole life)	44 (56.4)	49 (63.6)	93 (60.0)	
Stage[e], *n* (%)				0.50[b,f]
IIIB/C	2 (2.6)	—	2 (1.3)	
IVA/B	76 (97.4)	76 (98.7)	152 (98.1)	
Missing	—	1 (1.3)	1 (0.6)	
Use of prior platinum-based chemotherapy, *n* (%)	11 (14.1)	13 (16.9)	24 (15.5)	—
Prior EGFR TKI, *n* (%)				—
Erlotinib/gefitinib	57 (73.1)	57 (74.0)	114 (73.5)	
Afatinib/dacomitinib	21 (26.9)	19 (24.7)	40 (25.8)	
Other[g]	—	1 (1.3)	1 (0.6)	
EGFR mutation type, *n* (%)				0.30[b]
Exon 19 deletion	58 (74.4)	51 (66.2)	109 (70.3)	
Exon 21 L858R	20 (25.6)	26 (33.8)	46 (29.7)	
T790M testing material, *n* (%)				>0.99[b]
ctDNA	38 (48.7)	37 (48.1)	75 (48.4)	
Tumour	40 (51.3)	40 (51.9)	80 (51.6)	
Brain metastasis, *n* (%)				0.35[b]
Yes	13 (16.7)	8 (10.4)	21 (13.5)	
No	65 (83.3)	69 (89.6)	134 (86.5)	
Liver metastasis, *n* (%)				0.25[b]
Yes	14 (18.0)	8 (10.4)	22 (14.2)	
No	64 (82.0)	69 (89.6)	133 (85.8)	
Pleural effusion and ascites, *n* (%)				0.61[b]
Yes	7 (9.0)	9 (11.7)	16 (10.3)	
No	71 (91.0)	68 (88.3)	139 (89.7)	

Results -PFS

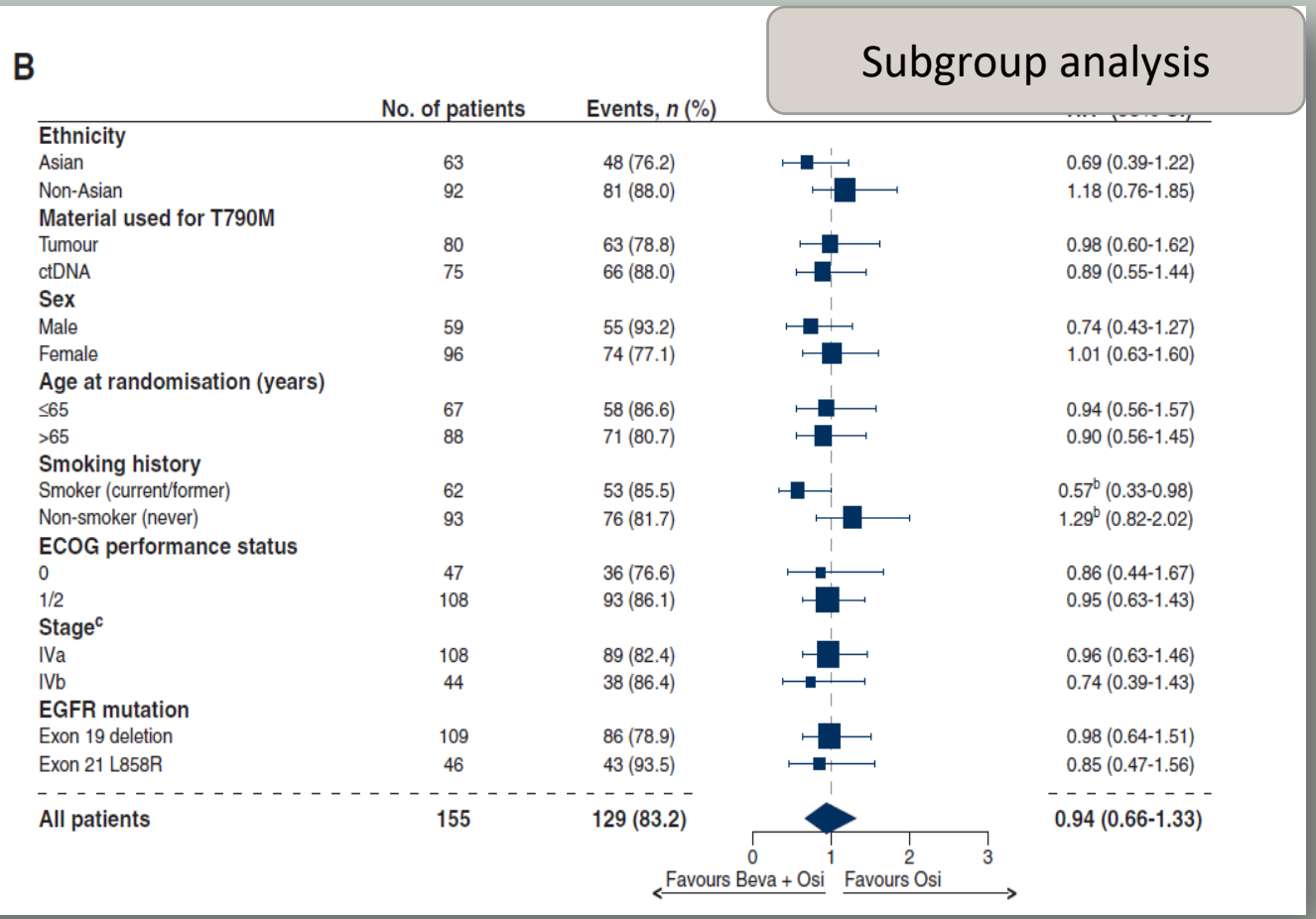


PFS

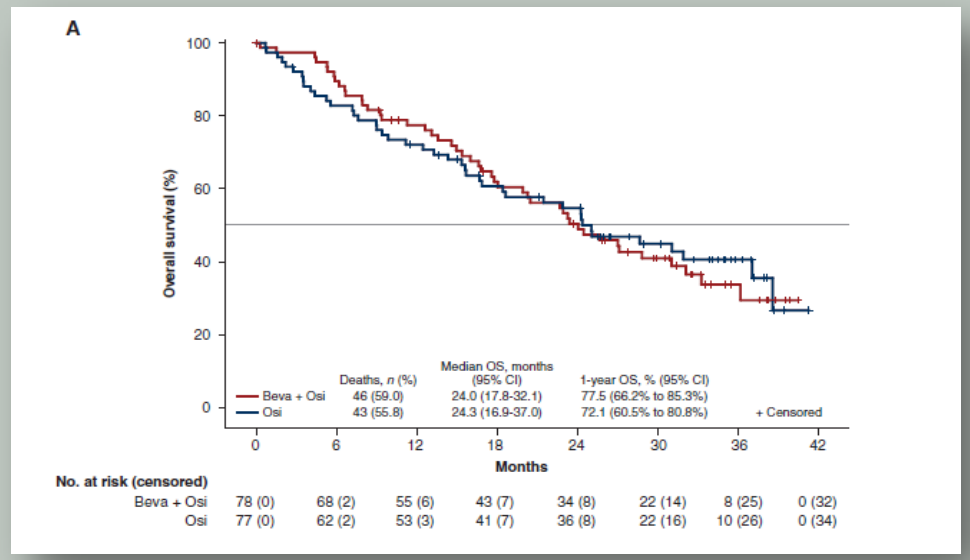


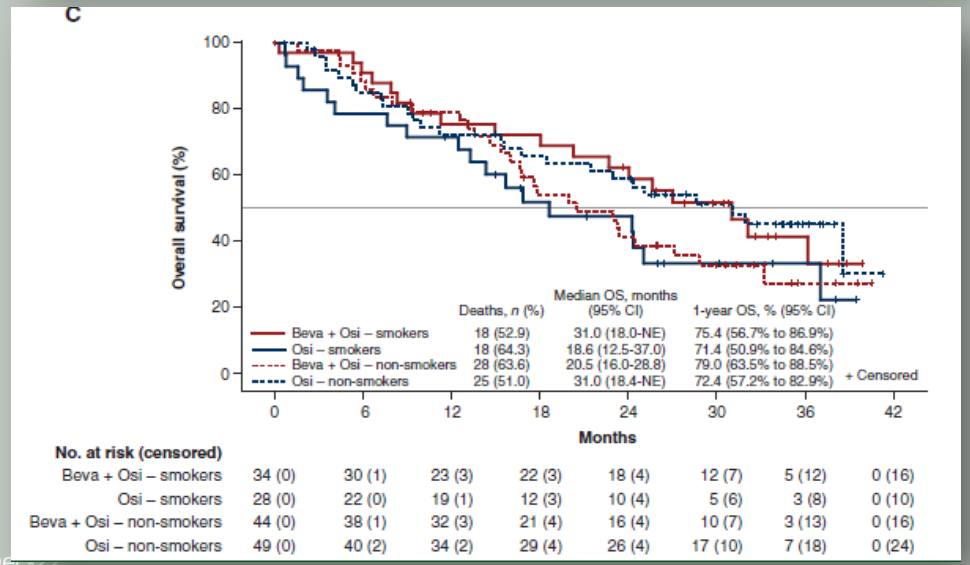
PFS
Smoking status

Subgroup analysis

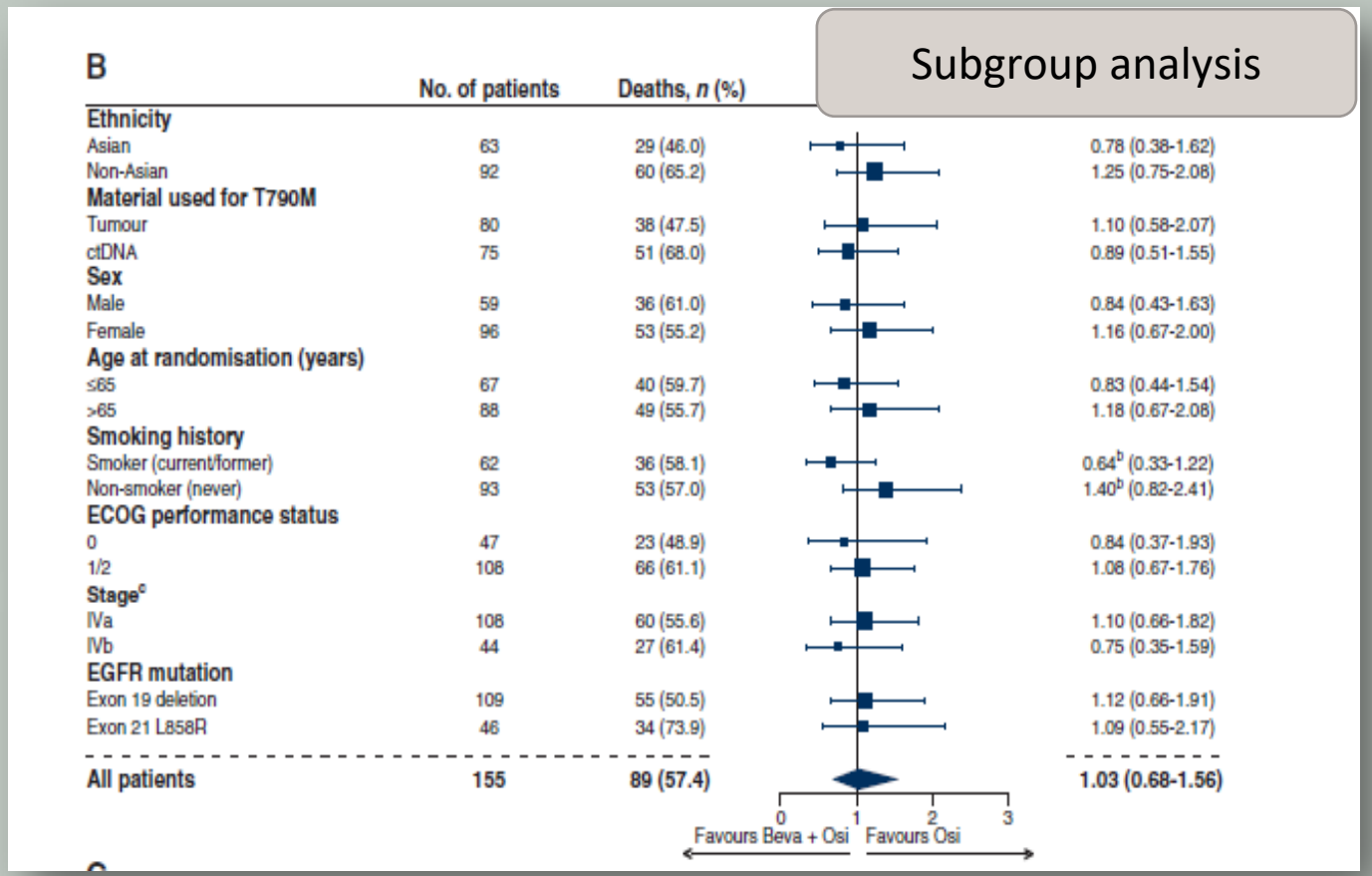


Results- OS





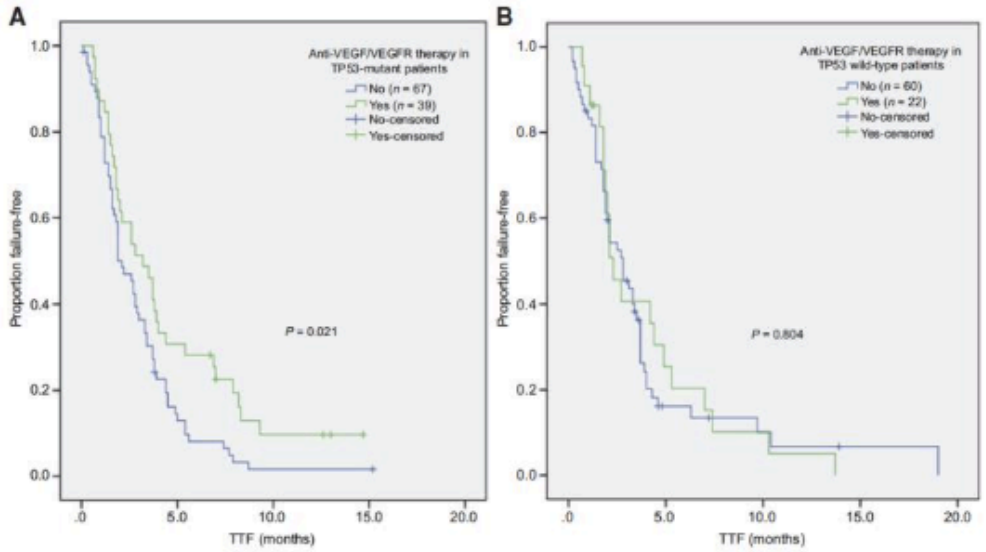
Subgroup analysis

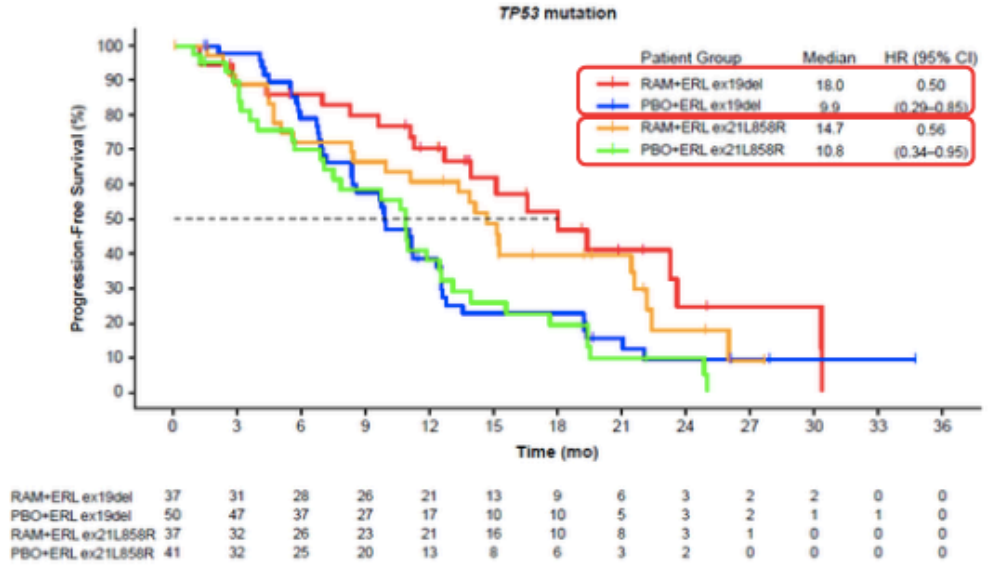


What is the basis of the enhanced signal observed in current/ former smokers in the BOOSTER trial?

Potential explanation

- Tobacco exposure produces genomic mutations in lung cancer, including *TP53* mutations.[1]
- *TP53* mutations are associated with improved outcomes with VEGF or VEGFR-inhibitors.[2-5]
- Translational studies are planned





Ross Soo, MB, BS; PhD; FRACP

1. Gibbons Mol Cancer Res 2013; 2. Schwaederle Cancer Res 2015; 3. Said Oncotarget 2013; 4. Wheler Mol Cancer Ther 2016; 5. Nakagawa Clin Cancer Res 2021

Results- Safety

Safety overview	Osimertinib/ bevacizumab *n* (%)	Osimertinib *n* (%)
Safety cohort	76	77
Patients experienced:		
Any AE	76 (100.0)	76 (98.7)
Treatment-related AEs	73 (96.1)	67 (87.0)
Treatment-related AEs grade 3-5	36 (47.4)	14 (18.2)
Treatment-related AEs leading to dose interruption[a]	23 (30.3)	7 (9.1)
Treatment-related AEs leading to dose reduction[b]	2 (2.6)	2 (2.6)
Treatment-related AEs leading to treatment discontinuation[c]	19 (25.0)	3 (3.9)
Treatment-related AEs leading to death	—	3 (3.9)

Treatment-related AEs occurring in ≥ 10% of patients:		
Diarrhoea	33 (43.4)	31 (40.3)
Rash acneiform	27 (35.5)	19 (24.7)
Fatigue	21 (27.6)	18 (23.4)
Proteinuria[d]	**34 (44.7)**	**1 (1.3)**
Hypertension[d]	**30 (39.5)**	**1 (1.3)**
Anorexia[d]	**20 (26.3)**	**8 (10.4)**
Dry skin	15 (19.7)	13 (16.9)
Oral mucositis[d]	**18 (23.7)**	**7 (9.1)**
Paronychia	12 (15.8)	10 (13.0)
Platelet count decreased	14 (18.4)	8 (10.4)
Pruritus	6 (7.9)	13 (16.9)
Lipase increased	9 (11.8)	7 (9.1)
Nausea	10 (13.2)	6 (7.8)

Conclusion

- The results suggest that the combination of bevacizumab and osimertinib is not associated with increased efficacy over osimertinib monotherapy in any clinical setting.

- Results from ongoing studies in the EGFR TKI-naive patient population receiving osimertinib with ramucirumab or with bevacizumab may further elucidate the role of this combination.

- Single-agent osimertinib remains the standard treatment in pretreated patients with EGFR-mutant NSCLC with acquired EGFR TKI resistance harbouring a T790M mutation.